Plasma ammonia levels in newborn infants admitted to an intensive care baby unit

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SUMMARY A fatal case associated with severe hyperammonaemia is described in which no urea cycle enzyme deficiency could be found. This prompted further investigation of blood ammonia levels in neonates admitted to the premature baby unit at Hammersmith Hospital. 102 specimens were taken from 42 babies within the first 3 weeks of life; the babies had a variety of clinical conditions. The mean ammonia level was 94·5 μmol/l (132·3 μg/100 ml) (range 32–255 μmol/l (44·8–357 μg/100 ml), SD ± 41·0). These results, although higher than the range for older babies in hospital, were not as high as in the baby with severe hyperammonaemia. Serial levels in 10 babies suggested that the range of blood ammonia levels was greatest in the first 2 weeks of life and narrowed considerably after this period. Great care is needed in collecting blood samples and measuring them if accurate results are to be obtained.

In 1977 a fatal case associated with severe hyperammonaemia was seen at Hammersmith Hospital. A plasma ammonia level taken 3 hours before death was 3000 μmol/l (4200 μg/100 ml) and cerebrospinal fluid taken shortly before death showed a level of 4000 μmol/l (5600 μg/100 ml). A liver biopsy was taken immediately after death, but no enzyme defect of the urea cycle could be found, and investigations for organic aciduria did not show an inborn error in branch-chain amino-acid metabolism. The clinical details are given below.

Three cases of severe hyperammonaemia in the neonatal period were reported by Pollack et al.1 and 5 more were reported by Ballard et al.2 In none of these babies was an enzyme defect observed, and no explanation for the cause could be found, but it was suspected that hyperammonaemia in the neonatal period might not be a rare occurrence.

Case history

A boy was born normally to a 22-year-old primigravida at 35 weeks’ gestation after spontaneous onset of labour. The Apgar score at one minute was 9. The birthweight was 2·58 kg (10th centile) and, apart from slight grunting, no abnormalities were noted initially. Milk feeds were started via nasogastric tube at 2 hours. The grunting continued for 14 hours and at this stage the baby was noted to be irritable but no cause for this was apparent.

At 24 hours his skin became mottled and he developed gasping respirations; blood sugar, urea and electrolytes, calcium, magnesium, and cerebrospinal fluid were all normal. The only abnormal finding was a metabolic acidosis. At 26 hours the baby had generalised convulsions which could not be controlled satisfactorily. In seeking an explanation for the deteriorating condition, a metabolic disorder was considered and a plasma ammonia level estimated with the result already mentioned above.

However, the urea cycle enzyme activities measured in the liver biopsy (taken shortly after death) by the method of Brown and Cohen,3 as described by Levin,4 did not show any defect. The analysis of urine for organic acids by gas chromatographic and mass spectrometric methods of Chalmers et al.5 also failed to show an inborn error of organic acid metabolism. The amino-acids were quantitatively examined in plasma, urine, and cerebrospinal fluid using an ion-exchange chromatographic LKB amino-acid analyser.6 The moderate increases in different amino-acids in the different specimens were typical of the sickest babies examined and did not suggest any specific metabolic disorder of amino-acid metabolism. Despite ventilatory assistance, the condition of the baby steadily deteriorated and he died at 39 hours.

At necropsy there was a small subdural haemorrhage over the left parieto-occipital region, blood clot in the cisterna magna, small bilateral
germinal layer haemorrhages, a small blood clot in the 4th ventricle, and bilateral necrosis of the periventricular tissue. In the lungs, there was evidence of inhaled material (epithelial squames and granular, foamy debris), and extensive hyaline membrane formation in the respiratory bronchioles.

The case prompted this investigation of plasma ammonia levels in neonates with a variety of clinical conditions and the results are now presented. The project was approved by the Royal Postgraduate Medical School ethics committee.

**Patients and methods**

42 babies admitted to the premature baby unit at Hammersmith Hospital were investigated. Their birthweights ranged from 740 to 3880 (mean 1823) g, and gestational ages (as assessed by Dubowitz Score\(^7\)) were between 27 and 41 (mean 32.4) weeks. 35 babies were preterm (less than 37 weeks) with 4 small for gestational age (below 10th centile); 3 of the 7 term babies were also small for gestational age.

Of the 42 babies, 14 died in the neonatal period. 27 had birth asphyxia (defined as an Apgar score of less than four within the first 5 minutes of life). In this group, 12 had respiratory distress syndrome (9 requiring ventilation), 1 had respiratory distress syndrome and convulsions, 3 recurrent apnoea and 1 apnoea and convulsions (these 4 were ventilated), 1 meconium aspiration and 1 meconium aspiration and convulsions, 1 pneumonia, 2 birth asphyxia associated with maternal sedation, 2 had convulsions, and 1 severe birth trauma. The remaining 2 had no problems other than birth asphyxia.

Of the 15 who did not have birth asphyxia, 11 had respiratory distress syndrome (5 required ventilating), 2 had apnoea (both ventilated), 1 convulsions secondary to hypoglycaemia, and 1 had no problems other than being preterm.

Blood samples were taken from indwelling umbilical artery catheters, via radial artery stabs or venepuncture when blood was required for tests connected with the management of the infants. 1.5 ml blood was collected in syringes containing heparin free of chlorocresol. The specimens were centrifuged and the plasma stored in liquid nitrogen until they were sent to St Bartholomew’s Hospital for ammonia levels to be measured. The specimens were sent in containers packed with dry ice. Measurements were made using an ammonia electrode as described by Park and Fenton.\(^8\)

Initial samples were taken on the day the baby was admitted to the unit and further samples were taken during the first 3 weeks of life. Altogether 105 measurements were made, 3 of the results have been excluded because of gross haemolysis of the blood samples.

**Results**

102 plasma ammonia levels were measured between day 1 and day 19 on the 42 babies. The mean level was 94.5 \(\mu\)mol/l (range 32--255 \(\mu\)mol/l, SD \(\pm\) 41.0). Fig. 1 shows the plasma ammonia levels plotted against postnatal ages.

80 results were obtained on 28 surviving babies and 22 on 14 babies who died in the neonatal period. The mean for the survivors was 89.1 \(\mu\)mol/l (range 32--192 \(\mu\)mol/l, SD \(\pm\) 36.5) and the mean for those who died was 114 \(\mu\)mol/l (range 44--255 \(\mu\)mol/l, SD \(\pm\) 36.7).

Figs 2 and 3 show the initial plasma ammonia levels for each baby (taken between days 1 and 4) plotted against gestational ages and birthweights.

10 surviving babies had at least 4 blood ammonia measurements taken during the first 19 days of life.
ammonia level for venous samples from neonates was 60 μmol/l (SD ± 20) and for capillary samples 86 μmol/l (SD ± 20). Measurements were made on 15 neonates.

Sanchez et al. observed ammonia levels greater than 90 μmol/l in 5 of 9 infants weighing less than 1000 g at birth, all were receiving assisted ventilation. They thought that these ammonia levels may have been contributed to by the use of blood products with a high ammonia content. However if the amount of ammonia administered by this method is calculated, it is unlikely to account for a considerably raised ammonia level.

There is some doubt about the correct procedure for collecting and preserving specimens. The methods adopted in this study are the result of work conducted over several years at St Bartholomew’s Hospital in adults. In normal adults there is little difference between ammonia levels measured from arterial and venous samples. However, differences can occur under several circumstances—for example when arterial ammonia levels are increasing rapidly the peripheral tissues, muscles, and brain actively take up ammonia, thereby lowering venous ammonia levels. Venous levels may rise above the arterial levels when tissues liberate ammonia as occurs with exercising muscle or during the recovery phase in some cases of hepatic coma. It is therefore conceivable that similar differences may occur in the neonate.

Capillary samples are less reliable for plasma ammonia measurements because contamination is difficult to avoid and levels may be falsely high. Care is needed to avoid gross haemolysis as red cell damage will also result in misleadingly high results. Blood should be collected into heparinised containers and it is important that the heparin is free from preservatives, such as chlorocresol, which may injure red blood cells and liberate ammonia. Unless measurements are to be made at once, the blood should be centrifuged within 30 minutes of collection and the plasma stored at −20°C overnight, or −70°C if a longer storage time is necessary. Specimens may be kept for 3 weeks at −70°C without adversely affecting the ammonia level.

There have been numerous methods for measuring ammonia in blood and this fact alone bears witness to the difficulties that have been encountered in the past. We prefer either an ion exchange column or a vapour phase ‘ion electrode’ for volatile base (EIL or Orion ammonia probe). Park and Fenton showed a good correlation between measurements made with these methods. We found that ion exchange resin in ‘batched’ shaking methods gave unreproducible results. Methods using glutamate dehydrogenase tended to lack sensitivity, and the older alkali

and these levels are shown in Fig. 4. The 2 babies with the highest levels (Cases 1 and 2) each had prolonged fits after severe birth asphyxia. In all 10 babies the range of results was far greater in the first week of life and the range had narrowed considerably 14 days later.

**Discussion**

Our studies suggest that ammonia levels in sick neonates (32–255 μmol/l) are well above the range that we accept as normal for children and adults (4–35 μmol/l). We have no experience of measuring ammonia levels in healthy preterm and term babies. However, using a microversion of the cation exchange column, Oberholzer et al. found the plasma

![Plasma ammonia levels plotted against birthweights.](http://adc.bmj.com/)

![Series of plasma ammonia levels in 10 babies in first 3 weeks of life.](http://adc.bmj.com/)
diffusion methods on which much of the older data are based are recognised to suffer from some ammonia artefact.

Ammonia is a normal constituent of body fluids. In the adult, exogenous ammonia is formed in the large intestine as a result of bacterial action on urea and other nitrogenous compounds. However, this cannot play a significant part in the early neonatal period until bacterial colonisation of the intestine has occurred. Therefore, in the neonate, the major contribution must result from the endogenous metabolism of glutamine, glutamate, and adenylylate. In animals, glutamine has also been shown to be taken up by the intestinal mucosa and hydrolysed, and this may be a significant source of ammonia in the sterile intestinal tract of the newborn infant. Under normal circumstances excess ammonia is rapidly removed by the liver.

Severe hyperammonaemia in the neonate has a similar clinical presentation whatever the cause. Principally this consists of: refusal of feeds, vomiting, lethargy, grunting respirations, fits preceding to coma and death in severe cases. Severe hyperammonaemia in the neonatal period is generally associated with inborn errors of metabolism. Since the report by Russell et al. of hyperammonaemia due to a urea cycle defect, there have been many reports of defects associated with this cycle. Errors in branch-chain amino-acid metabolism (especially methylmalonic acidemia and propionic acidemia) may also be associated with a very high plasma ammonia level. Other causes of hyperammonaemia include liver failure, and Reye's syndrome in the neonatal period was reported by Papageorgiou et al. Parenteral nutrition in preterm infants may result in hyperammonaemia. However, whether this is due to the high concentration of ammonia in protein hydrolysate or to transient metabolic deficiencies in sick, preterm infants is not certain. Ammonia levels have also been found to vary with different types of milk feed. Räihä et al. showed that levels varied with the quantity and quality of protein in milk. It is known that enzymes of the urea cycle are present in the human fetal liver at least by 16 weeks. However, the fetal liver is not able to adapt very well to a nitrogen load and this may also apply to the preterm neonate and account for raised ammonia levels. Anoxia is known to raise the ammonia level in isolated nervous tissue and raised levels also occur during shock states in animals. Hyperammonaemia has also been shown to occur after perinatal asphyxia and so it is conceivable that hypoxia due to respiratory problems in the neonate may contribute to the high levels. Although hypoxia has not been shown to result in raised levels in adults, the same may not be true of neonates as they can withstand a much greater degree of hypoxia than adults and a direct comparison cannot be made.

There may be a number of factors contributing to the raised level in the group of neonates that we studied. They had a variety of clinical conditions and it is not possible to say whether there is a relationship between birthweight or gestational age and ammonia level. A study on 'normal' preterm infants would first be required and then it may be possible to determine what clinical conditions, if any, are related to high ammonia levels.

The serial measurements in 10 babies showed a wider range over the first few days of life which had narrowed considerably by 14 days; at that time, all but 1 of the babies had recovered from their acute illness (1 still required mechanical ventilation because of recurrent apnoea). Two of the babies we studied had prolonged fits after severe birth asphyxia and in both cases the ammonia levels were in excess of 150 umol/l but fell once the fits had stopped. Both hypoxia and increased muscle activity may have played a part. Hyperammonaemia may result in the signs already mentioned but it is possible that persistently raised levels may have other side effects. It is interesting that a high level of plasma ammonia was shown to increase intracranial pressure in rhesus monkeys. An early increase in intracranial pressure in preterm infants was shown by Donn and ; and this they related to hypoxia. It may be that ammonia has a part to play in the aetiology of intraventricular haemorrhage in very low birthweight infants. However, whether these raised levels have any untoward side effects is not easy to determine. We were unable to find another baby with severe hyperammonaemia similar to that described at the beginning of this paper and we have been unable to account for such extreme increase in the level of plasma ammonia. Ballard et al. treated 4 patients successfully with exchange transfusion and peritoneal dialysis. It is clear that severe hyperammonaemia without an obvious metabolic defect may be more common than had previously been realised. It is important that clinicians should be aware of this syndrome and also that they be aware of the pitfalls in collecting specimens and methods of measurement if valid results are to be obtained.

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References


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